REPORT BY THE BIOEQUIVALENCE TASK FORCE

ON

RECOMMENDATIONS FROM THE BIOEQUIVALENCE HEARING CONDUCTED

BY THE FOOD AND DRUG ADMINISTRATION

September 29 - October 1, 1986

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I. EXECUTIVE SUMMARY

To foster public participation in FDA's bioequivalence program and in an effort to elicit data on claimed problems with the program and with generic drugs generally, the Agency sponsored a three day informal public hearing September 29 - October 1, 1986 in Washington D.C. The Hearing consisted of five sessions on topics related to the issue of bioequivalence of immediate release solid oral dosage form drug products. The topics were set forth in a Federal Register notice published June 27, 1986 announcing the Hearing and requesting interested parties to submit proposals to speak at the proceedings (51 FR 23476). The Hearing drew 50 speakers and over 800 participants.

Following the Hearing, FDA Commissioner Frank E. Young, M.D., Ph.D., and Deputy Commissioner John A. Norris, J.D., M.B.A. appointed a Task Force (see attachment 1) to analyze the issues raised at the Hearing and the comments submitted to the Public Docket, and to make recommendations for actions the Agency should take in response to those comments concerning the bioequivalence program.

The report of the Bioequivalence Hearing Task Force follows this summary. The Task Force has studied various aspects of the process used to evaluate the bioequivalence of immediate release solid oral dosage form drug products, and has carefully considered all material presented at the Hearing along with all material submitted to the Public Docket.

This summary discusses each issue and the recommendations made by the Task Force. The full report addresses the issues raised by topic rather than by session due to the significant overlap of topics and speakers' comments during the Hearing. Most of the issues raised fall into one of three topics: (1) design of bioequivalence studies, (2) decisional criteria for bioequivalence, or (3) Agency procedures and regulatory aspects of bioequivalence. The issues have been organized in this manner. A section containing the complete recommendations of the Task Force follows the discussion of the issues.

In this summary, each issue is identified, and the Task Force conclusions are described. The same numbering scheme is used in the summary and in the main body of the report for easy reference.

A. Design of Bioequivalence Studies

A-1. Are single dose studies adequate? Under what circumstance are multiple dose steady-state studies necessary to demonstrate bioequivalence?

TASK FORCE CONCLUSION The Task Force believes that as a general rule a single dose study is adequate. Multiple-dose studies should be performed only when a single-dose study is not a reliable indicator of bioavailability, e.g., because of the kinetics of the drug.

A-2. Should a three-period bioequivalence study with both a solution and reference product as reference standards be required?

TASK FORCE CONCLUSION The Task Force believes that a change to a 3-period bioequivalence study using a solution is not warranted for most cases. The usefulness of a solution as an anchor is warranted only when information about the relative bioavailability of a product is unknown or the bioavailability is known to be poor. A more clearly defined benefit should be shown to justify the increased costs associated with the three-period design before it is required in every case.

A-3. Does the use of normal volunteers adequately account for the potentially altered absorption capacity and metabolism of special populations?

TASK FORCE CONCLUSION The important question is not whether patients are different from volunteers, but whether, and when, these differences could cause two products that seem bioequivalent in normals to be bioinequivalent in a clinical setting. A search of the literature to identify these factors in patients revealed very few relevant publications. The Task Force believes that it is preferable to subject healthy people, rather than patients, to the rigors of blood sampling and other discomforts of bioequivalence testing. Moreover, use of patients would invariably increase intersubject variability and possibly intrasubject variability as well. Thus far there have been few, if any documented examples of problems associated with the use of normals to predict bioequivalence, although there have been relatively few rigorous attempts to document problems. The Task Force believes that at this time it remains appropriate to determine bioequivalence based on testing in healthy volunteers. The Agency recognizes the possibility that some conditions could affect bioavailability and is prepared to modify its position regarding the use of normal subjects if such a situation is adequately documented for a given drug. (see also recommendation 1)

A-4. Should bioequivalence studies include measuring of clinically active metabolites?

TASK FORCE CONCLUSION The Task Force believes that clinically active metabolites should be measured when they have significant pharmacologic activity.

A-5. Should FDA Develop individual criteria for each drug or class of drugs?

TASK FORCE CONCLUSION The Task Force endorses the current system of informal guidances on how to design and conduct studies prepared by the Division of Bioequivalence. This system of informal guidances promotes cooperation and consultation between FDA and industry, fosters scientific discussion and investigation, and permits the flexibility necessary to ensure that the guidances contain up-to-date scientific information and testing approaches. The general decisional criteria discussed elsewhere in this report (see B-1) could be better articulated and more widely publicized. Specific statistical methodology and review criteria could be incorporated into the guidance system or in another forum when appropriate.

A-6. Can dissolution testing assure bioequivalence? Should it be employed as a substitute for in vivo study in humans? Does adequate information exist to justify a waiver of in vivo studies based on dissolution alone? Should drugs be approved based on dissolution only without a relationship of in vitro data to in vivo performance?

TASK FORCE CONCLUSIONS The Task Force believes there is not yet evidence to show that any particular dissolution pattern alone will assure bioequivalence. Dissolution testing can be used for drugs where there is a known in vivo/in vitro relationship, and is used for pre-1962 drugs not suspected of having, or not likely to have, a bioavailability problem. (see attachment 7) For all other solid oral drugs, an in vivo bioequivalence study on the drug product is required to support at least one strength of the product.

The Task Force believes that dissolution testing is important in assuring lot-to-lot uniformity, and in supporting minor alterations to drug products (see 21 CFR 320.22(d)). Also, it is FDA policy that if a product meets in vivo bioequivalence study requirements at one strength, and the formulations of additional strengths are proportional to the strength tested in the in vivo bioequivalence study, and the additional strengths meet dissolution requirements, then further in vivo bioequivalence studies are not required for the additional strengths unless there is evidence of safety or efficacy problems. This policy applies to generic and innovator products. The Task Force believes these policies are sound, but does not recommend expanding the use of in vitro testing beyond these limits.

A-7. Do or should bioequivalence studies consider the effect of excipients on bioavailability of drug products? What is the likelihood of an excipient causing toxicity in a patient?

TASK FORCE CONCLUSION The Task Force agrees that the rare incidence of allergies and toxicity to excipients may pose a problem for a few patients. Information on excipients for all drug products is currently being addressed by the PMA and the PA with their voluntary labeling guidelines and this information will help enable patients to be alerted to an allergenic potential. The effect of excipients on bioavailability is assessed by current bioequivalence studies.

A-8. How should FDA assure lot-to-lot uniformity? Are in vivo bioequivalence studies necessary to approve all formulation changes?

TASK FORCE CONCLUSION The Task Force believes that dissolution testing is appropriate for assuring lot-to-lot uniformity. The more difficult question is the extent to which particular changes in formulation may affect the bioavailability of a drug product. The FDA may waive the requirement for submission of evidence of in vivo bioavailability under certain conditions for solid oral dosage forms. Generally, a waiver is granted for a 'minor' change in formulation (e.g., change in color). (See draft guidance for explanation at attachment 9). The dividing line between a minor and a major reformulation is not always clear, however, and even a series of minor reformulations could have the same implication as a major reformulation. (see also recommendation 2)

A-9. Should an alternate study design be considered as the standard for bioequivalence testing to determine intrasubject variability?

TASK FORCE CONCLUSION Requiring a second study for bioequivalence determinations is not justified. The use of bioequivalence studies with an alternate study design is being considered. (see also recommendation 3)

B. Decisional Criteria for Bioequivalence

B-1. Should the current equivalence criteria be changed? What do these differences mean clinically?

TASK FORCE CONCLUSION The Task Force favors the use of a 90% confidence interval based on the two one-sided t-test approach as the best available method for evaluating bioequivalence. The Task Force concludes that some drugs or drug classes may require tighter limits than the generally applied ± 20% rule. These situations must be identified on the basis of clinical evidence demonstrating a need to tighten the generally applied standard. Such evidence could include, for example, a prospective clinical study demonstrating that the usual criteria for bioequivalence measurements are not stringent enough. The Task Force also concludes that the requirement that the entire 90% confidence interval lie within the limits of ± 20% effectively precludes true differences in means beyond those limits. The Task Force believes that there may be merit to the consultant's proposal for an additional criteria, because it would add significantly to the assurance of the bioequivalence of generic drugs, and would also preclude the unusual case of a real difference beyond ± 10%. However, the Task Force does not believe it is necessary to require an additional criteria beyond the current requirements. (see also recommendation 4)

B-2. Could the ± 20% requirement lead to differences in products of 40-50%?

TASK FORCE CONCLUSION The Task Force notes that for post-1962 drugs approved over a two-year period under the Waxman-Hatch bill, the mean bioavailability difference between the generic and innovator product is 3.5% (see the discussion under B-1). Additionally, 80% of the values for drugs approved since 1984 were within ± 5.0% of the reference drug value. (see attachment 11)

B-3. Should the use of the 75/75 rule as a decisional tool be dropped by FDA? Should confidence intervals be used as the principal decision criterion for bioequivalence studies?

TASK FORCE CONCLUSION The Agency agrees with the consensus that the 75/75 rule should be dropped. The Task Force favors the use of a 90% confidence interval based on the two one-sided t-test approach to evaluate bioequivalence. This involves determining the confidence interval for the ratio of means using a modified t-test method. (see attachment 10)

B-4. Is product to product variability within an acceptable range? Should the Agency expend resources to answer this question, and if so, how should it be determined?

TASK FORCE CONCLUSION The Task Force believes that current requirements are adequate to assure the quality and uniformity of all drug products. However, the variability among drug products deserves further study. (see also recommendation 5)

B-5. How should outlying data be treated in bioequivalence analyses?

TASK FORCE CONCLUSION The Task Force believes that neither testimony at the Hearing, nor any currently available document adequately addresses these issues. (see also recommendation 6)

C. Agency Procedures and Regulatory Aspects of Bioequivalence

C-1. Should bioequivalence decisional criteria be published using notice and comment rulemaking?

TASK FORCE CONCLUSION The Task Force believes the Agency can make clearer the decisional criteria it employs to determine bioequivalence. The specific guidances on how to design and conduct a bioequivalence study are good examples of the Agency's ability to convey this kind of information to the regulated industry.

The Task Force does not agree, however, that notice and comment rulemaking is the appropriate mechanism for disseminating information about the decisional criteria. In this regard, we believe notice and comment rulemaking is too slow a process to accommodate new and evolving statistical and biopharmaceutical scientific methods and changes based on new information and experience. It is also difficult to write a meaningful regulation in this area since bioequivalence is often a matter of judgment. To ensure the flexibility necessary to keep Agency criteria current, a method other than rulemaking is recommended. (see attachments 8 & 12)

The Agency could publish a formal guideline specifying the decisional criteria used to evaluate bioequivalence studies. This guideline would be subject to public comment and would commit the Agency to follow the guideline. Under current administrative procedures, formal guidelines can be modified more quickly than can regulations. However, these formal guidelines still must be announced by FEDERAL REGISTER publication.

Several speakers at the Hearing recommended including more information about the decisional criteria in the Orange Book. We suggest that a guideline on the bioequivalence decisional criteria could either be a part of the Orange Book, a supplement to the Orange Book, a separate publication, or perhaps some combination of those publications listed above. Others at the Hearing voiced concern regarding the cost of the Orange Book. Before including a guideline into the Orange Book, we must consider these concerns because the cost of the Orange Book is based on its total number of pages. (see also recommendation 7)

C-2. Should FDA establish an advisory panel to advise the Agency on bioequivalence issues?

TASK FORCE CONCLUSION The Task Force agrees with the principle of obtaining views about bioequivalence from outside the Agency especially concerning general bioequivalence issues. The Agency currently employs individual consultants on an ad hoc basis for guidance on a variety of issues including bioequivalence. The Agency also sponsors or cosponsors a number of meetings that address bioequivalence issues as well as others. The Task Force believes the Agency should continue these practices. In addition, the Agency should consider other ways to broaden outside input, e.g., augmenting existing standing advisory committees with biopharmaceutic experts. (see also recommendation 8)

C-3. Have there been therapeutic failures with approved generic products? Is the current adverse drug reaction monitoring program adequately detecting therapeutic failures? How useful is form 1639 for reporting therapeutic failures?

TASK FORCE CONCLUSION The Task Force concludes that FDA should enhance current procedures to better detect and evaluate reports of therapeutic failures that could be indicative of failure of a product. FDA should fully investigate possible inequivalence only when there is good evidence of a problem, and not on unsupported anecdotes. The medical community and the manufacturers should be encouraged to submit reports of therapeutic inequivalence with as much detail as possible, including blood level data. (see also recommendation 9)

C-4. Can FDA's therapeutic equivalence list, (the Orange Book), be revised to show whether an AB rating is based on in vivo or in vitro testing? Can the Orange Book also be made more widely available and at a lower cost?

TASK FORCE CONCLUSION The Task Force believes the Orange Book should be modified so that it is possible to determine by the drug code the basis by which drugs were rated. (see also recommendations 10 and 11)

C-5. Should the patient and the physician be notified by the pharmacist when generic substitution occurs? Is there a problem of indiscriminant substitution of products by pharmacists in states even when 'no substitution' is requested, and are products not rated as bioequivalent being substituted? Should FDA get involved in these issues?

TASK FORCE CONCLUSION FDA does not regulate the practice of pharmacy or medicine. Regulation of these professions is properly within a state's purview. The states are free to use FDA's bioequivalence determinations and therapeutic equivalence evaluations or not use them. Depending on individual product selection laws, some states develop their own formularies of interchangeable drug products. Each state has its own requirements regarding substitution. Thirty-eight states and the District of Columbia have permissive substitution and 12 have mandatory substitution. Forty states require patient consent for substitution. Commissioner Young stated that

"...we can in no way substitute federal judgment for state responsibility, and in no way substitute, in my opinion, state and federal responsibility for the responsibility of the physician. To do so would be, in my opinion, utter folly."

All states prohibit pharmacists from making substitutions of products when "DAW" (Dispense as Written) or some similar instruction is written by the physician. The Task Force concludes that allegations of violations of these prohibitions are appropriately within the jurisdiction of the states. Unauthorized substitution should be brought to the attention of the appropriate state authorities for any necessary action. These issues are not federal issues. (see also recommendations 12 and 13)

C-6. What should the requirements be for approving better formulated copies of poorly bioavailable innovator products?

TASK FORCE CONCLUSION The Task Force is aware of only a handful of approved products on the market that are considered to be poorly bioavailable. This does not appear to be a major and immediate public health problem because:

1) each of the poorly formulated products was approved on the basis of clinical investigations demonstrating its safety and efficacy; and

2) each of these poorly formulated products has been on the market for several years without documented safety and efficacy problems.

FDA is prepared to approve generic products where the innovator is poorly available and the generic product matches the bioavailability of a more fully bioavailable formulation and produces blood levels equivalent to those of the innovator product when given at a lower dose. Such a product would be considered bioinequivalent to the innovator product under the petition provisions [Section 505(j)(2)(C)] of the Act.

C-7. What would be the significance of one documented generic failure?

TASK FORCE CONCLUSION The Task Force concludes that there is no reason to doubt the fundamental principle that drug products delivering comparable blood levels of a therapeutic moiety in bioequivalence tests in normals will generally yield comparable therapeutic results. There are known differences among patients, such as gut transit time or gastric pH that could, combined with differences between products, such as pH dependency of dissolution, theoretically yield differences in performance of products in certain patients. Whether this hypothesis actually is manifested clinically in any significant way has not been shown. A distinction must be drawn between a single case of a patient who does not respond to a drug product and evidence that a drug product is not performing. Virtually all products are, from time to time, the subject of isolated reports of

therapeutic failures. The Agency looks particularly for patterns of such reports or cases which may indicate a generalized problem with a drug product or a batch of the product. The documentation of a single instance of clinical inequivalence does not, in the Task Force's view, undermine the much wider experience that shows bioequivalence testing to be an excellent predictor of clinical performance. A product failure, on the other hand, would necessitate that the Agency investigate thoroughly and take steps to deal with the particular case and others that might arise from similar circumstances.

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II. TASK FORCE RECOMMENDATIONS - ACTION ITEMS

The Task Force recommends that the Agency take the following actions based on its discussion of issues that were addressed at the Bioequivalence Hearing and from items submitted to the Public Docket:

1. The Task Force recommends that the Agency be prepared to pursue, in house or extramurally, any credible leads suggesting patient factors not tested for currently which might lead to differences in bioequivalence. The Agency would welcome the conduct of such studies by the industry. (see A-3)

2. The Task Force recommends that a public meeting be held or some other forum be used, e.g., a Federal Register notice soliciting information and comment to allow discussion of such questions regarding reformulation changes. (see A-8)

3. The Task Force recommends that the Division of Biometrics undertake a study of alternative study designs to address the need for any changes in current protocol design. (see A-9)

4. The Task Force recommends that the Agency make more widely available the criteria it uses to make bioequivalence determinations, as well as any exceptions to those criteria, e.g., where the standards are more or less stringent for particular drugs for documented clinical reasons. The Task Force recommends that the Agency publish procedures under which drugs or classes of drugs would be added to or deleted from the list of drugs subject to either more strict or less strict criteria than the general rule. Also, the Task Force recommends that the Agency consider the feasibility of adding an additional nonstatistical criteria for the mean difference of AUC to be $\pm$ 10%. However, the Task Force does not believe that such an additional criteria beyond the current requirements is necessary for assuring the bioequivalence of generic drugs. (see B-1)

5. The Task Force recommends that the Division of Biometrics gather data and develop statistical methodology to consider whether a problem exists regarding product variability. Appropriate action will be taken, should a problem be discovered. (see B-4)

6. The Task Force recommends that the Division of Biometrics undertake a comprehensive evaluation of the treatment of outliers. (see B-5)

7. The Task Force recommends that the Agency publish full information about the bioequivalence evaluation procedures and decisional criteria, either in the form of a formal guideline, or as a supplement or companion piece to the Orange Book. (see C-1)

8. The Task Force recognizes that there is a significant interest in obtaining more outside input on bioequivalence issues and recommends that the Agency explore further this possibility. (see C-2)

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III. BACKGROUND AND EVALUATION PROCEDURES

A. Background

Broadly speaking, bioequivalence involves the comparison of the bioavailability of two drug products, bioavailability being defined as the rate and extent to which an active drug ingredient is absorbed and becomes available at the site of drug action. Two drug products are generally said to be bioinequivalent if, under similar experimental conditions, the rate or extent of absorption of one differs significantly from that of the other.

Problems of bioinequivalence have undoubtedly existed since there first was more than one product containing the same active ingredient. Awareness of these problems, however, is a relatively recent phenomenon, arising in the late sixties and early seventies. As the science of biopharmaceutics evolved, attention was focused on the clinical implications of differences in the bioavailability of drug products made by different firms, or of different batches of a drug product made by a single firm.

The bioavailability of a drug product can be affected by a number of biological and pharmaceutical factors. For example, for an orally administered drug, bioavailability is dependent upon factors such as the area in the gastrointestinal tract from which the drug is absorbed, the dissolution and stability of the drug in the gastrointestinal tract, the rate at which the drug is absorbed from the gastrointestinal tract, and the rate of metabolism of the drug in the intestinal wall and liver. In turn, these biological factors interact with the specific pharmaceutical characteristics of the product, including the physical structure and particle size or surface area of the active drug ingredient, the quantity and characteristics of inactive ingredients, the coating of a tablet or capsule, and the compression applied to produce a tablet. Variations in any of these factors, either from batch to batch of one manufacturer or from the product of one manufacturer to that of another, can produce variations in bioavailability and thus bioinequivalence.

In 1970 FDA began to systematically require evidence of "biological availability" in applications submitted for approval of certain new drugs. In April 1974, a Drug Bioequivalence Study Panel, formed by the Congress of the United States, Office of Technology Assessment (OTA), began to examine the relationships between the chemical and therapeutic equivalence of drug products and to assess the capability of current technology to determine - without therapeutic trials in human subjects - whether drug products with the same physical and chemical composition produce comparable therapeutic effects. The OTA Report was released in July, 1974. The OTA Report recommended, among other things, that drug products for which bioequivalence is considered critical be identified as bioequivalent only after a showing has been made insuring their bioequivalence.

In June, 1975 (40 FR 26157) the Agency published a proposed rule in the Federal Register (FR) to require, among other things, the submission of bioavailability data in certain new drug applications. These regulations were published as a final rule in the FR of January 7, 1977 (42 FR 1638). These regulations became effective on July 7, 1977 and are currently codified in 21 CFR Part 320.

During the decade of the seventies when the science of biopharmaceutics was evolving, when the awareness of potential bioinequivalence problems was becoming more widespread and when the Agency began to formally regulate this area, a controversy was growing between two segments of the pharmaceutical industry. The controversy centered around questions of: (1) whether products manufactured by generic drug manufacturers were comparable in quality to those manufactured by the so-called pioneer or innovator drug firms, and, (2) whether the generic copies of the innovator drug products could be used by the public with confidence that they would have comparable therapeutic effect. (see attachment 2) During the first part of the 1980's this controversy between the generic and innovator drug firms intensified and in September of 1984 reached new levels with the passage of the Drug Price Competition and Patent Term Restoration Act (the 1984 Amendments to the Food, Drug and Cosmetic Act). The 1984 Amendments provided, among others things, a quick and efficient method for approving generic copies of virtually all innovator drug products not protected by patents. The controversy continued to intensify during the two years following enactment of the 1984 Amendments and some began to call into question the Agency's methods and procedures for determining the bioequivalence of drug products. (see attachment 3) It was during this time that the Agency decided to hold a Bioequivalence Hearing to provide a forum for all interested persons to express their views on the scientific principles and procedures the Agency uses to make a finding of bioequivalence between immediate release solid oral dosage forms.

The public Hearing was held by the FDA from September 29 - October 1, 1986 in Washington D.C., chaired by FDA Commissioner Frank E. Young, M.D., Ph.D., Deputy Commissioner John A. Norris, J.D., M.B.A. and three outside experts on bioequivalence. Over 50 formal presentations were made at the Hearing by representatives from, among others, various segments of the pharmaceutical industry, professional societies, governmental agencies, and academia. A transcript of the Hearing was made from an audio recording. (see attachment 4)

The Agency invited interested persons to submit written comments concerning the issues discussed at the Bioequivalence Hearing. Persons who made presentations at the Hearing were invited to submit comments to supplement their presentations or make additional points. Subsequently, the Agency formed a task force to evaluate the presentations, comments, questions, and suggestions made at the 3-day hearing, and to review all comments submitted to the public docket. This group identified the significant issues raised at the Hearing and in the comments and drafted a report. Comments on the report were received from two of the three consultants who participated in the Hearing. The report that follows includes recommendations for actions the Task Force considers appropriate.

B. Evaluation Procedures

The current approach to the review of a bioequivalence study is to assess whether the results of the study demonstrate the products to be equivalent with respect to average bioavailability. The Division of Bioequivalence decides which measures of bioavailability (e.g., AUC, Cmax, etc.) will be considered, and what the equivalence criterion will be for each measure. The Agency statistical review determines for each measure whether the data supports a finding of bioequivalence.

The statistical method currently in use in the Agency consists of carrying out two appropriate one-sided statistical tests, one to verify that the bioavailability of the test product is not too low, and one to show that it is not too high. This procedure has good statistical properties and currently is the method of choice for assessing equivalence of average bioavailability. This procedure has essentially replaced the analysis of variance approach with its consideration of power and the '75/75 rule'. These procedures are discussed in more detail in attachment 5.

IV. BIOEQUIVALENCE HEARING - Issues and Task Force Conclusions

A. Design of Bioequivalence Studies

A-1. ARE SINGLE DOSE STUDIES ADEQUATE? UNDER WHAT CIRCUMSTANCES ARE MULTIPLE DOSE STEADY-STATE STUDIES NECESSARY TO DEMONSTRATE BIOEQUIVALENCE?

The question of whether single dose or multiple dose studies are generally appropriate was discussed in depth by three presenters at the Hearing (pp. 5-9, 27-33, and 75-84).* It was also discussed to a lesser degree by at least six other presenters (pp. 92, 119, 128, 138, 441, and 750). There was a consensus among the speakers that while some drugs may require a multiple dose study, for most drugs a single dose study is usually adequate. A summary of representative comments follows:

- Single dose study results are generally adequate. (Weintraub, p. 119)
- Single dose studies are recommended generally for immediate release formulations with known linear pharmacokinetics. (Benet, p. 128)
- If most of the drug is gone by the time one administers the second dose, what is gained from a steady state study? (Temple, p. 83)
- If a study fails a single dose study, it is possible that it will pass a steady state study, but if it fails a steady state study, it is not likely to pass on single dose. (Perkal, p. 9)

Others commented, however, that there may be special situations where the pharmacokinetics of the drug will require a multiple dose study. For example:

- for classes of drugs with first pass metabolism as well as those influenced by changes in gastrointestinal pH and motility. (Weintraub, p. 119)
- when drug and/or metabolite have nonlinear pharmacokinetics and greater than predicted accumulation. (Benet, p. 128)

Multiple dose studies allow the subjects to be at a steady state level of drug accumulation, metabolism and excretion at the time the bioavailability parameters are determined. It is unlikely that a drug with a short half-life will accumulate in a steady state situation, such that a multiple dose and single dose study will yield dissimilar results. For immediate release formulations with linear kinetics where blood levels are readily measurable and there is no unusual variability, single dose studies are generally adequate. However, for drugs with nonlinear kinetics, or with blood levels too low to measure accurately, a multiple dose study may be needed. The Agency recognizes that more discussion is needed on this issue.

The Agency may require a multiple-dose study to determine the bioavailability of a drug when:

1. there is a difference in the rate of absorption, but not in the extent of absorption;
2. there is excessive variability in bioavailability from subject to subject;

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*Page references in Section IV are to the pages in the official transcript. (attachment 4)

3. the concentration of the active drug ingredient or therapeutic moiety in the blood from a single dose is too low for accurate determination by the analytical method; or

4. the drug product is a controlled release dosage form.

TASK FORCE CONCLUSION

The Task Force believes that as a general rule a single dose study is adequate. Multiple-dose studies should be performed only when a single-dose study is not a reliable indicator of bioavailability, e.g., because of the kinetics of the drug.

A-2. SHOULD A THREE-PERIOD BIOEQUIVALENCE STUDY WITH BOTH A SOLUTION AND REFERENCE PRODUCT AS REFERENCE STANDARDS BE REQUIRED?

Several speakers suggested, with varying degrees of enthusiasm, the use of a three-period study with a solution as an anchor. (Meyer, p. 93, Cabana, p. 95, Barr, p. 754)

A third leg of a bioequivalence study that employs a solution can provide information about the relative bioavailability of both the test and reference solid dosage forms, and can be useful to point out situations where the formulation of the products could be improved. It can also warn about possible "upward drift" of bioavailability, e.g., when the reference product shows improved bioavailability. Three-period studies, however, are not essential to assess bioequivalence in every case.

TASK FORCE CONCLUSION

The Task Force believes that a change to a 3-period bioequivalence study using a solution is not warranted for most cases. The usefulness of a solution as an anchor is warranted only when information about the relative bioavailability of a product is unknown or the bioavailability is known to be poor. A more clearly defined benefit should be shown to justify the increased costs associated with the three-period design before it is required in every case.

A-3. DOES THE USE OF NORMAL VOLUNTEERS ADEQUATELY ACCOUNT FOR THE POTENTIALLY ALTERED ABSORPTION CAPACITY AND METABOLISM OF SPECIAL POPULATIONS?

A number of speakers at the Hearing addressed the question of whether the use of normal volunteers is appropriate for bioequivalence testing:

- If there is a known bioavailability difference between patients and healthy volunteers, then the study must be conducted in patients. (Benet, p. 126)

Do normal volunteers adequately reflect patient populations?

- Food or concomitant medications can affect the bioavailability of different formulations and tests on healthy volunteers may not always detect this. (Weintraub, p. 119)

- The typical healthy subject is not representative of the real world nor is the data obtained valid for our patient populations. (Goldstein, p. 441-2)

However, others pointed out the disadvantages in using patients for studies:

- Patients cannot be controlled like normal subjects and studies on patients are thus imprecise. (Perkal, p. 5-8)

- Patients are fairly heterogeneous with a wide variety of characteristics which may ultimately make it difficult to verify study results. With no inclusion criteria, the data could be variable and difficult to interpret. (Meyer, p. 89)

- In patients, there are factors including age, weight, concurrent medication, pregnancy among others which increase the difficulty in predicting Cmax or AUC during treatment. (Van Hoert, p. 86-7)

One speaker presented data in which a group of patients were identified who appeared to fail on the generic version of tolazamide and do well on the innovator's product. Clinical data did indeed show significant changes in various clinical parameters, which returned to normal when the patient was returned to the innovator product. The innovator firm, however, concluded nothing substantial from their followup bioavailability study with the generic drug in question. The manufacturer of the generic product also did a prospective clinical study looking for differences in patient response to the generic and innovator product to answer the allegations, and observed different results regarding the rate of absorption and clinical effects seen. A summary of the results of this study is attached to the report. (see attachment 6)

The Task Force believes that it would be useful to identify factors in patients that might lead to different responses in patients to drugs that seemed bioequivalent in normals. A search of the literature reveals only a few publications on the subject. One obvious possibility would be the presence of gastric hypoacidity in some patients which might produce differences in bioavailability between products whose dissolution was pH dependent. FDA has contracted for a study to explore the effect of stomach pH on bioavailability (the University of Tennessee study).

TASK FORCE CONCLUSION

The important question is not whether patients are different from volunteers, but whether, and when, these differences could cause two products that seem bioequivalent in normals to be bioinequivalent in a clinical setting. A search of the literature to identify these factors in patients revealed very few relevant publications.

The Task Force believes that it is preferable to subject healthy people, rather than patients, to the rigors of blood sampling and other discomforts of bioequivalence testing. Moreover, use of patients would invariably increase intersubject variability and possibly intrasubject variability as well. Thus far there have been few, if any documented examples of problems associated with the use of normals to predict bioequivalence, although there have been relatively few rigorous attempts to document problems. The Task Force believes that at this time it remains appropriate to determine bioequivalence based on testing in healthy volunteers. The Agency recognizes the possibility that some conditions could affect bioavailability and is prepared to modify its position regarding the use of normal subjects if such a situation is adequately documented for a given drug.

TASK FORCE RECOMMENDATION

The Task Force recommends that the Agency be prepared to pursue in house or extramurally any credible leads suggesting patient factors not tested for currently which might lead to differences in bioequivalence. The Agency would welcome the conduct of such studies by the industry.

A-4. SHOULD BIOEQUIVALENCE STUDIES INCLUDE MEASURING OF CLINICALLY ACTIVE METABOLITES?

Several speakers agreed with current Agency policy, which is to require the measurement of major metabolites of a drug ingredient or therapeutic moiety in bioequivalence studies. A summary of remarks follows:

- If the metabolite is clinically significantly active in terms of efficacy or toxicity, the metabolites should be measured. (Benet, p. 127)

- PMA believes that evaluation of active metabolites may be indicated in which each has its own discreet pharmacokinetic or pharmacodynamic profile. (Weintraub, p. 120)

The Agency currently requires the measurement of metabolites with significant pharmacologic activity especially when the parent compound has a very short half life or if the blood levels of the parent drug are very low. The measurement of metabolites adds relatively little to the cost of a study.

TASK FORCE CONCLUSION

The Task Force believes that clinically active metabolites should be measured when they have significant pharmacologic activity.

A-5. SHOULD FDA DEVELOP INDIVIDUAL CRITERIA FOR EACH DRUG OR CLASS OF DRUGS?

- Testing methodologies should be individualized to specifically address the biopharmaceutic and physicochemical characteristics unique to each chemical entity. (Weintraub, p. 121).

- Individualized bioequivalence criteria should be developed by FDA at the time of ANDA eligibility. (Lavy, p. 316).

There are two issues here. First is the issue of how one should design and conduct a bioequivalence study. The second is under what criteria one should measure the results of the study.

FDA already has a series of individual guidances which define the individual testing procedures for a number of different drugs or classes of drugs. These guidances provide assistance to the applicant in general protocol development and in selecting a methodology for assaying the active ingredient. These guidances, however, do not include statistical criteria.

A second issue deals with the decisional criteria for bioequivalence and with the statistical criteria to be used to determine if an in vivo study on a specific drug product demonstrate bioequivalence to the reference product. The general criteria used by FDA, 20% for upper and lower boundaries of the 90% confidence interval, is discussed in detail in part B of this report. These criteria assure that real differences of more than ± 20% are extremely unlikely to occur. But even if they do, they are not likely to be clinically important. FDA is prepared to use a more stringent criterion if differences of this size are shown to be clinically significant, or a less stringent criterion for a drug with a large inherent variability where no clinical significance is shown.

The criteria for review and approval of a generic drug product are based on the statute and regulations that require a generic product to be bioequivalent to its listed drug in rate and extent of absorption.

TASK FORCE CONCLUSION

The Task Force endorses the current system of informal guidances on how to design and conduct studies prepared by the Division of Bioequivalence. This system of informal guidances promotes cooperation and consultation between FDA and industry, fosters scientific discussion and investigation, and permits the flexibility necessary to ensure that the guidances contain up-to-date scientific information and testing approaches. The general decisional criteria discussed elsewhere in this report (see B-1) could be better articulated and more widely publicized. Specific statistical methodology and review criteria could be incorporated into the guidance system or in another forum when appropriate.

A-6. CAN DISSOLUTION TESTING ASSURE BIOEQUIVALENCE? SHOULD IT BE EMPLOYED AS A SUBSTITUTE FOR IN VIVO STUDY IN HUMANS? DOES ADEQUATE INFORMATION EXIST TO JUSTIFY A WAIVER OF IN VIVO STUDIES BASED ON DISSOLUTION ALONE? SHOULD DRUGS BE APPROVED BASED ON DISSOLUTION ONLY WITHOUT A RELATIONSHIP OF IN VITRO DATA TO IN VIVO PERFORMANCE?

There was extensive discussion at the Hearing concerning the use of in vitro dissolution testing as a substitute for in vivo studies and whether dissolution testing could substitute for in vivo testing. A summary of remarks follows:

- The primary use of dissolution testing lies in the screening and quality control of pharmaceutical formulations and as a basis for validating selected alterations in a previously approved formulation. (Carrigan, p. 165).

- In vitro dissolution is not a substitute for in vivo bioavailability. (Benet, p. 171).

- In vitro tests can fail to predict clinical performance and one needs to validate in vitro tests with biological data. (Lasagna, p. 280).

- FDA should not waive in vivo data for other than a minor modification of an approved process. (Schimmel, p. 593).

- A clinically acceptable article can look quite bad on any typical dissolution test. (Grady, p. 261).

- Strong correlations between in vivo absorption and in vitro dissolution parameters are necessary before any quantitative projections regarding the bioavailability of a test product can be made. (Rocci, p. 208).

A particular concern was raised about drugs having dissolution that is pH dependent.

- An in vivo/in vitro correlation is not predictable if dissolution of the tablet pH dependent. (Beckett, p. 157-163). (The Task Force notes that FDA is currently studying the effect of pH dependent formulations on bioavailability under contract with the University of Tennessee).

Current requirements provide for the use of in vitro dissolution testing in place of in vivo data when older drugs (those first approved before 1962) do not pose an actual or potential bioequivalence problem as defined in the 1977 regulations (21 CFR 320), or when an in vivo/in vitro correlation has been shown. For example, the Agency has determined that an in vitro/in vivo correlation exists for prednisone. This decision was based on bioavailability studies conducted on a variety of prednisone products sponsored under FDA contract. These studies established an in vitro and in vivo correlation with a variety of in vitro apparatus and media.

TASK FORCE CONCLUSIONS

The Task Force believes there is not yet evidence to show that any particular dissolution pattern alone will assure bioequivalence. Dissolution testing can be used for drugs where there is a known in vivo/in vitro relationship, and is used for pre-1962 drugs not suspected of having, or not likely to have, a bioavailability problem. (see attachment 7) For all other solid oral drugs, an in vivo bioequivalence study on the drug product is required to support at least one strength of the product.

The Task Force believes that dissolution testing is important in assuring lot-to-lot uniformity, and in supporting minor alterations to drug products (see 21 CFR 320.22(d)). Also, it is FDA policy that if a product meets in vivo bioequivalence study requirements at one strength, and the formulations of additional strengths are proportional to the strength tested in the in vivo bioequivalence study, and the additional strengths meet dissolution requirements, then further in vivo bioequivalence studies are not required for the additional strengths unless there is evidence of safety or efficacy problems. This policy applies to generic and innovator products. The Task Force believes these policies are sound, but does not recommend expanding the use of in vitro testing beyond these limits.

A-7. DO OR SHOULD BIOEQUIVALENCE STUDIES CONSIDER THE EFFECT OF EXCIPIENTS ON BIOAVAILABILITY OF DRUG PRODUCTS? WHAT IS THE LIKELIHOOD OF AN EXCIPIENT CAUSING TOXICITY IN A PATIENT?

In considering these two questions, the following points were made:

- Bioequivalence testing does not measure the therapeutic consequences of excipients, e.g., allergic potential in an individual. (Weintraub, p. 122)
- The potential for adverse reaction from so-called inactive excipients is rare. (Strom, p. 645)
- The problem, is interchanging one product with another and not knowing that it may contain a different inactive ingredient which could cause toxicity or an allergic reaction in a particular person. (Schwartz, p. 666)

The first question of potential toxicity of excipients is beyond the scope of the Hearing. With respect to the second question on the effect on bioequivalence, the studies carried out address the effects of excipients and any other feature of the formulation on bioavailability. This point was addressed in an Agency petition response to Hoffmann-La Roche. (see attachment 8)

TASK FORCE CONCLUSION

The Task Force agrees that the rare incidence of allergies and toxicity to excipients may pose a problem for a few patients. Information on excipients for all drug products is currently being addressed by the Pharmaceutical Manufacturers Association (PMA) and the Proprietary Association (PA) with their voluntary labeling guidelines and this information will help enable patients to be alerted to an allergenic potential. The effect of excipients on bioavailability is assessed by current bioequivalence studies.

A-8. HOW SHOULD FDA ASSURE LOT-TO-LOT UNIFORMITY? ARE IN VIVO BIOEQUIVALENCE STUDIES NECESSARY TO APPROVE ALL FORMULATION CHANGES?

- You need bioequivalence testing as a basis for approval. We establish the relationship between dissolution and bioavailability by evaluating lot-to-lot uniformity so that dissolution can then be used within the range to assure bioequivalence. If you establish an acceptable dissolution rate range where bioavailability doesn't change, then as long as all your lots fall within that range, you could say that dissolution could be utilized to assure lot-to-lot. (Albert, p. 182-83)

TASK FORCE CONCLUSION

The Task Force believes that dissolution testing is appropriate for assuring lot-to-lot uniformity. The more difficult question is the extent to which particular changes in formulation may affect the bioavailability of a drug product. The FDA may waive the requirement for submission of evidence of in vivo bioavailability under certain conditions for solid oral dosage forms. Generally, a waiver is granted for a 'minor' change in formulation (e.g., change in color). (See draft guidance for explanation at attachment 9). The dividing line between a minor and a major reformulation is not always clear, however, and even a series of minor reformulations could have the same implication as a major reformulation.

TASK FORCE RECOMMENDATION

The Task Force recommends that a public meeting be held or some other forum be used, e.g., a Federal Register notice soliciting information and comment to allow discussion of such questions regarding reformulation changes.

The following comment to the docket raises an issue that was not fully discussed at the Hearing.

One comment urged the Agency to make public the criteria used for authorizing waivers of in vivo studies for multiple strength drug products and reformulations.

The Division of Bioequivalence currently determines whether or not the generic product has a formulation that is similar to the innovator product which is used to waive an in vivo bioequivalence study. This policy grants waivers for multiple strengths of a single drug product as well as for reformulations. The Division of Bioequivalence is preparing a guideline describing these criteria which will be made available to the general public upon completion. (see attachment 9)

A-9. SHOULD AN ALTERNATE STUDY DESIGN BE CONSIDERED AS THE STANDARD FOR BIOEQUIVALENCE TESTING TO DETERMINE INTRASUBJECT VARIABILITY?

- ".... Normal crossover designs are generally recommended. ... If a drug has high variability, or if a known intrasubject variability exists, then a more elaborate study design is desirable..." (Benet, p. 324).

- "I urge more widespread use of stable isotopes and certainly, as mentioned frequently, a greater consideration of replicate designs in those cases where intrasubject variability is a major problem." (Gibaldi, p. 748)

- "...two products can have the same average bioavailability but the one with the smaller and more consistent intra- and intersubject variability would be more desirable. And in some circumstances it may be appropriate to design studies to evaluate this." (Rodda, p. 453).

Ordinarily, a two-period crossover design is an adequate design for comparing the bioavailability of two products. If however, variability within subjects in such a study is large, it may be helpful to measure the within-subject variability directly by using a replicate design in which patients are given the same treatment more than once. Three- or four-period crossover studies with two treatments could be employed for a short time to gather data about whether such designs might prove superior (attachment 10). The Agency is considering this concept and will ask for public comments, if it decides to implement it. Designs using stable isotopes can also be used to assess intrasubject variability.

The Task Force notes, however, that it is not clear that greater precision in the assessment of variability would be useful or whether there are, in fact, situations in which the mean bioavailability of two products is the same but the variability is truly greater with one product than the other. It appears that any residual error in the statistical analysis of the study is more likely to be related to product variability rather than to subject variability.

Some speakers likened the need for two independent bioequivalence studies to FDA's requirement for two adequate and well-controlled clinical studies to establish safety and efficacy for a new drug. However, there are important distinctions between the two types of studies.

First, a bioequivalence study involves a drug substance having well defined pharmacokinetics. It involves a measurement that is straightforward, is repeated frequently (to permit assessment of its consistency) and is blinded and bias free. Moreover, poor technique, should it occur, leads to excessive variance and will result in failure to meet the confidence interval requirements.

On the other hand, clinical studies are normally designed to establish, among other things, the safety and effectiveness of a previously unevaluated drug substance. They involve no firm prior expectations (unless there was an earlier study). And, there is sufficient uncertainty and potential bias in the clinical setting to require that clinical effectiveness findings be replicated and regularly repeated as they build on previous experience and data.

TASK FORCE CONCLUSION

Requiring a second study for bioequivalence determinations is not justified. The use of bioequivalence studies with an alternate study design is being considered.

TASK FORCE RECOMMENDATION

The Task Force recommends that the Division of Biometrics undertake a study of alternative study designs to address the need for any changes in current protocol design.

B. Decisional Criteria for Bioequivalence

B-1. SHOULD THE CURRENT EQUIVALENCE CRITERIA BE CHANGED? WHAT DO THESE DIFFERENCES MEAN CLINICALLY?

Regarding change in the acceptance criteria:

- Change the acceptance criteria to ± 10%. (Meyer, p. 293)
- Exclude the ± 20% Rule and instead impose individual bioequivalence criteria for each drug. (Lavy, pp. 313 and 316)
- Conduct intrasubject variabilities (sic) on the same dosages to verify particular interactions in a effort to evaluate ± 10% (Garrett, pp. 298 and 529)
- The ± 20% Rule is an acceptable starting point. (Benet, p. 323)
- Apply more narrow bioequivalence limits to drugs with toxicity problems or narrow therapeutic windows. (Benet, p. 324)

Regarding clinical significance:

- Address the relationship between blood level, variations in blood level of the drug and the pharmacologic effectiveness of the drugs. (Lipson, p. 695)
- Can clinicians pick up a difference of 20% or 30% in something so difficult to see? (Barr, p. 671)

There was consensus at the Hearing that differences of less than 20% in AUC and Cmax between products in normal subjects are unlikely to be clinically significant in patients. Clinical studies of effectiveness have difficulty detecting differences in dose of even 50-100%. Few drugs are given on a mg per kg basis to account for weight differences and few drugs have their dosage adjusted in actual clinical practice for factors that may affect blood concentrations in individuals. Thus, the variability inherent in medical practice and biological variation may cause plasma levels to vary in individuals by much more than 20%.

Moreover, current practice in the evaluation of bioequivalence makes a true difference in means as large as 20% very unlikely. In the vast majority of cases, the actual difference between the means will be much smaller. Indeed, the observed mean difference between the bioavailability of generic and innovator products for post-1962 drugs approved over a two year period under the Waxman-Hatch Act has been only 3.5% (attachment 11). These differences are very small, especially compared to the kinds of differences that can ordinarily be detected clinically, as is discussed above. It must be appreciated that an observed difference between test mean and reference mean of 20% would not be acceptable. Under current review procedures, the 90% confidence interval for the ratio of the test product mean AUC to that of the innovator must lie entirely within the interval (0.80, 1.20). The same is true for the ratio of test to innovator Cmax. This is a far more stringent test than merely requiring that the observed ratio of means be within the interval and accounts for sample size and study variability, both intra- and intersubject. It should be stated that the rule puts a limit on the ratio of the true, underlying product means. The rule is not intended to prevent occurrence of occasionally greater ratios for individual subjects.

The 20% bioequivalence rule can be and has been modified for drugs with a narrow therapeutic window, e.g. warfarin. The Agency has also used modified criteria for drugs with a wider therapeutic window, e.g., some psychotropic drugs which are difficult to measure from a bioequivalence standpoint. Because experts conclude that differences of less than 20% in mean AUC between brand name and generics are rarely unacceptable, FDA has established procedures to assure with high probability that the true mean AUC between brand name and generic products do not differ by more than 20%. A medical evaluation is made if the same assurance cannot be given for Cmax to ascertain whether this difference may be therapeutically significant.

One speaker simulated a ± 20% variation by administering a dose of drug that was 20% above and 20% below a standard dose of chlorpropamide to normal volunteers, in an effort to determine whether such differences would lead to significant differences in relevant clinical parameters. (Kradjan, p.393). The study, conducted in normals did not demonstrate any difference in blood glucose or C-peptide, even though the 20% variation in dose led to AUC values that varied from 75% to 130% of the standard dose. The study has been repeated in patients, but the Agency has yet to receive the data.

One consultant recommended that FDA substitute a requirement that the mean AUC of the test product be within 10% of the mean AUC of the reference product. The Task Force believes that this requirement is less stringent than the currently employed criterion based on confidence intervals. The Task Force feels that as an additional requirement - over and above the currently employed criterion - it would further reassure the public of the comparability of the innovator and generic products. However, the Task Force does not believe that such an additional criteria beyond the current requirements is necessary. Further, from the data used to prepare the graph in attachment 11, it can be estimated that only about 1% of generic drugs approved with current procedures would fail to pass this additional criterion. If adopted, this additional requirement would be applied prospectively and would also apply to reformulations of innovator products.

TASK FORCE CONCLUSION

The Task Force favors the use of a 90% confidence interval based on the two one-sided t-test approach as the best available method for evaluating bioequivalence. The Task Force concludes that some drugs or drug classes may require tighter limits than the generally applied ± 20% rule. These situations must be identified on the basis of clinical evidence demonstrating a need to tighten the generally applied standard. Such evidence could include, for example, a prospective clinical study demonstrating that the usual criteria for bioequivalence measurements are not stringent enough. The Task Force also concludes that the requirement that the entire 90% confidence interval lie within the limits of ± 20% effectively precludes true differences in means beyond those limits. The Task Force believes that there may be merit to the consultant's proposal for an additional criteria, because it would add significantly to the assurance of the bioequivalence of generic drugs, and would also preclude the unusual case of a real difference beyond ± 10%. However, the Task Force does not believe it is necessary to require an additional criteria beyond the current requirements.

TASK FORCE RECOMMENDATION

The Task Force recommends that the Agency make more widely available the criteria it uses to make bioequivalence determinations, as well as any exceptions to those criteria, e.g., where the standards are more or less stringent for particular drugs for documented clinical reasons. The Task Force recommends that the Agency publish procedures under which drugs or classes of drugs would be added to or deleted from the list of drugs subject to either more strict or less strict criteria than the general rule. Also, the Task Force recommends that the Agency explore the option of adding an additional nonstatistical criteria for the mean difference of AUC to be ± 10%. However, the Task Force does not believe that such an additional criteria beyond the current requirements is necessary for assuring the bioequivalence of generic drugs.

B-2. COULD THE ± 20% REQUIREMENT LEAD TO DIFFERENCES IN PRODUCTS OF 40-50%?

The notion that a 40% or 50% difference actually occurs between the mean values of two generic products is based on the erroneous impression that products with bioavailability ratios of 0.80 and 1.20 would be approved. With such differences in mean AUCs, the requirements involving confidence intervals would not be met.

As one consultant stated:

- "... theoretically [or potentially] the ± 20% difference between a test product and reference product, that has been allowed in the past, could conceivably result in two test products differing by as much as 40 or 50% from each other. This could occur only under special circumstances (the reference must have low bioavailability) and then rarely. The current practice of requiring confidence intervals will virtually eliminate this possibility." (Barr, see attachment 14)

- A statement that FDA allows drug products to enter the market as generic equivalents with 80% to 120% of innovator's products ignores the fact that such a theoretical product must not be statistically different from the innovator's product. To assume that a product would be approved by FDA that could be 80% different and 120% different is not feasible. (Benet, p. 323)

TASK FORCE CONCLUSION

The Task Force notes that for post-1962 drugs approved over a two-year period under the Waxman-Hatch bill, the mean bioavailability difference between the generic and innovator product is 3.5% (see the discussion under B-1). Additionally, 80% of the values for drugs approved since 1984 were within ± 5.0% of the reference drug value. (see attachment 11)

B-3. SHOULD THE USE OF THE 75/75 RULE AS A DECISIONAL TOOL BE DROPPED BY FDA? SHOULD CONFIDENCE INTERVALS BE USED AS THE PRINCIPAL DECISION CRITERION FOR BIOEQUIVALENCE STUDIES?

- The limitations of the 75/125 Rule are that it's not based on rigorous statistical tests. (Meyer, p. 294)
- The 75/75 rule ... may be preliminarily valid for estimating bioequivalence, but it can't be taken seriously for a final conclusive statement. (Garrett, p. 750)
- The 75/75 Rule has undesirable performance characteristics when the test and reference products have hypothetically equal means. (Rodda, p. 450)

The 75/75 rule was developed initially to normalize the data of some studies in a simple way when it seemed that ratios of test to reference values were unusually variable. However, a number of people questioned the statistical basis for the 75/75 rule. Its poor performance at predicting bioequivalence has long been known. The development of sophisticated statistical analysis and alternate methods to assess bioequivalence has led to discontinuance of the use of the 75/75 rule as a decisional tool. Thus, the Agency agrees with the consensus that the 75/75 rule should no longer be used to approve generic products. (see attachment 10)

TASK FORCE CONCLUSION

The Agency agrees with the consensus that the 75/75 rule should be dropped. The Task Force favors the use of a 90% confidence interval based on the two one-sided t-test approach to evaluate bioequivalence. This involves determining the confidence interval for the ratio of means using a modified t-test method. (see attachment 10)

B-4. IS PRODUCT TO PRODUCT VARIABILITY WITHIN AN ACCEPTABLE RANGE, I.E., COMPARABLE TO LOT TO LOT VARIABILITY?

Several speakers addressed the issue of product to product vs. lot to lot variability (pp. 148, 297, 458, 503-34). A representative comment was that: "The variability seen between products is no different than the variability seen between different lots of the innovator." (Goldberg, p. 507)

The USP requirements for uniformity of dosage units permit significant variation in the potency between individual dosage units. On a batch to batch basis, the potency of individual units can fluctuate by as much as 15% to 25%. The Agency also currently requires all firms, brand name or generic, to use the same dissolution testing as well as a number of other tests as quality control measures to assure the lot to lot uniformity of its products. Based on limited data available to FDA, the product to product variability in blood levels among bioequivalent drug products on the average does not appear to be significantly greater than variability seen between different lots of the same product of a single manufacturer.

TASK FORCE CONCLUSION

The Task Force believes that current requirements are adequate to assure the quality and uniformity of all drug products. However, the variability among drug products deserves further study.

TASK FORCE RECOMMENDATION

The Task Force recommends that the Division of Biometrics gather data and develop statistical methodology to consider whether a problem exists regarding product variability. Appropriate action will be taken, should a problem be discovered.

B-5. HOW SHOULD OUTLYING DATA BE TREATED IN BIOEQUIVALENCE ANALYSES?

Several questions were raised regarding the methods for determining outliers and how they should be treated. (pp. 429-33; 455)

The identification and treatment of outliers in bioequivalence studies deserves more attention than it has received to date. Removing certain subjects from consideration in a study because their data do not conform to the rest of the data may affect the validity of the study. In most cases, one cannot determine whether the apparently nonconforming data is due to a laboratory error, data transcription error, or other causes unrelated to bioequivalence. This argues against removing the data.

TASK FORCE CONCLUSION

The Task Force believes that neither testimony at the Hearing, nor any currently available document adequately addresses these issues.

TASK FORCE RECOMMENDATION

The Task Force recommends that the Division of Biometrics undertake a comprehensive evaluation of the treatment of outliers.

C. Agency Procedures and Regulatory Aspects of Bioequivalence

C-1. SHOULD BIOEQUIVALENCE DECISIONAL CRITERIA BE PUBLISHED USING NOTICE AND COMMENT RULEMAKING?

The decisional criteria or statistical criteria used to determine bioequivalence should not be confused with the guidances issued by FDA providing informal advice on how to design and conduct a study. See, for example, section A-5 in Part IV. The decisional criteria used by FDA to determine bioequivalence are discussed in Part IV B of this report -- Decisional Criteria for Bioequivalence. The issue under consideration here is whether the Agency should publish the statistical or decisional criteria using the notice and comment rulemaking process, i.e., codify these criteria in binding regulations. A representative sampling of the comments at the Hearing follow:

- Notice and comment rulemaking is the proper and lawful approach; guidelines should be qualified with proper legal input. (Benet, p. 605)
- The Drug Price Competition and Patent Term Restoration Act requires that bioequivalence criteria be enacted according to notice and comment provisions of the Administrative Procedures Act. (Schimmel, p. 594)
- By using guidance instead of regulation, we are giving the scientific community more flexibility to devise the best study possible and reflect changing scientific knowledge. (Bass, p. 687-88)
- There seems to be a concern that good, fair standards be developed. (Young, p. 758)

TASK FORCE CONCLUSION

The Task Force believes the Agency can make clearer the decisional criteria it employs to determine bioequivalence. The specific guidances on how to design and conduct a bioequivalence study are good examples of the Agency's ability to convey this kind of information to the regulated industry.

The Task Force does not agree, however, that notice and comment rulemaking is the appropriate mechanism for disseminating information about the decisional criteria. In this regard, we believe notice and comment rulemaking is too slow a process to accommodate new and evolving statistical and biopharmaceutical scientific methods and changes based on new information and experience. It is also difficult to write a meaningful regulation in this area since bioequivalence is often a matter of judgment. To ensure the flexibility necessary to keep Agency criteria current, a method other than rulemaking is recommended. (see attachments 8 & 12)

The Agency could publish a formal guideline specifying the decisional criteria used to evaluate bioequivalence studies. This guideline would be subject to public comment and would commit the Agency to follow the guideline. Under current administrative procedures, formal guidelines can be modified more quickly than can regulations. However, these formal guidelines still must be announced by FEDERAL REGISTER publication.

Several speakers at the Hearing recommended including more information about the decisional criteria in the Orange Book (pp. 442, 579-92, 743-44). We suggest that a guideline on the bioequivalence decisional criteria could either be a part of the Orange Book, a supplement to the Orange Book, a separate publication, or perhaps some combination of those publications listed above. Others at the Hearing voiced concern regarding the cost of the Orange Book. Before including a guideline into the Orange Book, we must consider these concerns because the cost of the Orange Book is based on its total number of pages.

The following comment to the docket raises an issue that was not fully discussed at the Hearing.

One comment suggested that the statistical techniques favored by the Agency be made available in a guideline or guidance.

The statistical review of a bioequivalence study is an assessment of whether the results of the study demonstrate the products to be equivalent with respect to average bioavailability. The Division of Bioequivalence decides as to which measures of bioavailability (e.g. AUC, Cmax, etc.) will be considered, and what the equivalence criterion will be for each measure. The Agency uses the statistical review to determine for each measure whether the data supports a finding of bioequivalence. (see section B, C-1, attachment 10)

TASK FORCE RECOMMENDATION

The Task Force recommends that the Agency publish full information about the bioequivalence evaluation procedures and decisional criteria, either in the form of a formal guideline, or as a supplement or companion piece to the Orange Book.

C-2. SHOULD FDA ESTABLISH AN ADVISORY PANEL TO ADVISE THE AGENCY ON BIOEQUIVALENCE ISSUES?

Several speakers advocated establishing a bioequivalence Advisory Panel. A representative comment was:

- There must be both analytical-biopharmaceutic and clinical expertise, on such panels. (Benet, p. 607)

The scope of duties for an Advisory Panel would, as one speaker commented, include:

- Assessing the need for additional studies in special populations and to recommend studies to assure a scientific basis for a decision. A panel should consider the relevance of a particular formulation, the relevance of a peak height, the relevance of an Area Under the Curve, or relevance of a pharmacodynamic measure, and the relevance of a therapeutic index. They would never look at any submissions. (AAPS Task Force, p. 127, Benet, 608-09)

TASK FORCE CONCLUSION

The Task Force agrees with the principle of obtaining views about bioequivalence from outside the Agency especially concerning general bioequivalence issues. The Agency currently employs individual consultants on an ad hoc basis for guidance on a variety of issues, including bioequivalence. The Agency also sponsors or cosponsors a number of meetings that address bioequivalence issues as well as others. The Task Force believes the Agency should continue these practices. In addition, the Agency should consider other ways to broaden outside input, e.g., augmenting existing standing advisory committees with biopharmaceutic experts.

TASK FORCE RECOMMENDATION

The Task Force recognizes that there is a significant interest in obtaining more outside input on bioequivalence issues and recommends that the Agency explore further this possibility.

C-3. HAVE THERE BEEN THERAPEUTIC FAILURES WITH APPROVED GENERIC PRODUCTS? IS THE CURRENT ADVERSE DRUG REACTION MONITORING PROGRAM ADEQUATELY DETECTING THERAPEUTIC FAILURES? HOW USEFUL IS FORM 1639 FOR REPORTING THERAPEUTIC FAILURES?

These issues were somewhat controversial.

Two physicians related personal experiences with generic drug products that they believed were therapeutically inequivalent (O'Connor, p. 677-86 and Stoffer, p. 707-38; see Section VI, appendix). Of these cases, the Task Force has been unable to obtain further documentation. Had adequate documentation been provided to the Agency by Drs. O'Connor or Stoffer, these problems would have been investigated through a bioequivalence study. To date, there has been no instances in which clinical inequivalence has been documented and verified for approved products.

The following comments are representative of the response at the Hearing to these allegations.

- You were giving testimonials. An objective appraiser needs documented proof. I can't take what you gave me on faith. You've got to give me documentation. (Garrett, p. 682)

- There is overall concern about patients, and I question whether someone can legitimately make these kind of unsubstantiated assaults on these products without documented proof. (Brown, p. 681)

A number of speakers at the Hearing expressed doubt about whether the current adverse reaction reporting systems were likely to be effective in detecting therapeutic failures due to bioinequivalence:

- The 1639 form is not applicable to a person wishing to report an ineffectiveness drug problem to the Agency. (Meyer, p. 579)

- Does the ADR system monitor pharmacologic failure? Pharmacologic failure is currently only reported if it is associated with serious unlabeled reactions or increased incidence of failure. It seems that FDA is discouraging reporting these cases except for the examples listed above. (Cadieux, p. 619)

- I agree to some extent that it's not a good form for collecting lack of efficacy reports. The 1639 form is designed to record the report of a single patient undergoing a toxic reaction and lack of efficacy is not toxicity. (Faich, p. 583)

- To say the system is perfect because we have not detected any clinical failures is naive and probably not good science. (Barr, p. 755)

The Adverse Drug Reaction (ADR) reporting system is most effective when it detects an adverse event that is known to be relatively unlikely to occur in the absence of a drug effect (e.g., liver injury, hematologic injury) and when the event occurs in close time relationship to use of the drug. The system is not good at detecting drug-induced events when those events are common in the absence of a drug in the population treated.

Therapeutic failures are a relatively common component of most drug treatment, even when the drug is not changed. Blood pressures can rise on previously effective therapy; heart failure can worsen on a stable digoxin/diuretic regimen; seizures can break through, for example, phenytoin. A report of a single instance of failure is, therefore, almost impossible to interpret unless there is a deliberate attempt to study it further with blood level data or an on-off-on-off procedure. Estimated rates of failure would also be extremely difficult to derive from ADR data.

In general, we believe that if a product fails, it will led to more than one report, so we are not primarily concerned with one idiosyncratic report. However, in order to spot as early as possible any widespread problems such as problems with an entire lot, the agency will in some cases, look at single, isolated, well documented cases. Additionally, the Agency recognizes that important knowledge may be gained from the study an isolated case.

There have been some efforts recently to stimulate reporting to FDA's voluntary ADR system of adverse reactions to generic products. FDA's voluntary system is based upon spontaneous reporting by physicians and other health practitioners. If adverse reaction reports to a spontaneous reporting system are encouraged or stimulated with respect to a competitor's drug products, a distortion of that system will result. Thus, FDA has opposed and will continue to oppose, any attempts to solicit or otherwise stimulate adverse reaction reports for any product. These activities, and unknown differences in reporting rates for brand and generic drugs make rate comparisons very speculative.

TASK FORCE CONCLUSION

The Task Force concludes that FDA should enhance current procedures to better detect and evaluate reports of therapeutic failures that could be indicative of failure of a product. FDA should fully investigate possible inequivalence only when there is good evidence of a problem, and not on unsupported anecdotes. The medical community and the manufacturers should be encouraged to submit reports of therapeutic inequivalence with as much detail as possible, including blood level data.

TASK FORCE RECOMMENDATION

The Task Force recommends that detailed plans for identifying signals or clusters of possible important instances of product failure from the ADR reporting system be developed. These plans should indicate how and when these signals will be communicated to the appropriate Agency components. The Task Force recommends that a policy be developed to outline how, when, and by whom signals should be investigated, the role of laboratory testing, requiring repeat bioequivalence testing, field work to investigate individual cases, and the responsibilities of the several offices involved. The Task Force recommends that the current ADR regulations be modified to require that reports be submitted to the Agency to aid in accomplishing these recommendations.

C-4. CAN FDA's THERAPEUTIC EQUIVALENCE LIST, (THE ORANGE BOOK), BE REVISED TO SHOW WHETHER AN AB RATING IS BASED ON IN VIVO OR IN VITRO TESTING? CAN THE ORANGE BOOK ALSO BE MADE MORE WIDELY AVAILABLE AND AT A LOWER COST?

Although most drugs rated AB were done so on the basis of in vivo bioequivalence tests, there are drug products rated AB on the basis of in vitro dissolution testing alone. Many people have argued that the basis of this decision should be made clear to users of the Orange Book. The 7th edition of the Orange Book says of "A" coded drugs:

> for those DESI drug products containing active ingredients having actual or potential bioequivalence problems and for post-1962 drug products, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence supporting the bioequivalence of the product to a selected standard product.

This evidence may be an in vivo bioavailability study or an in vitro dissolution rate study or both, depending upon the drug. These products are designated AB.

TASK FORCE CONCLUSIONS

The Task Force believes the Orange Book should be modified so that it is possible to determine by the drug code the basis by which drugs were rated.

TASK FORCE RECOMMENDATION

The Task Force recommends that a method be devised to identify the drugs now rated AB on the basis of dissolution alone, and that the category AB be reserved for drugs that have been approved on the basis of an *in vivo* bioequivalence study.

The Task Force also recommends that the Orange Book be more widely advertised to pharmacists. This could be accomplished by working more closely with the states. Efforts to decrease the cost should be explored. This could be accomplished by publishing an abbreviated version of the list alone, by selling the Orange Book without the monthly supplements, or by enlisting the assistance of a private organization to make the book available at a lower cost.

C-5. SHOULD THE PATIENT AND THE PHYSICIAN BE NOTIFIED BY THE PHARMACIST WHEN GENERIC SUBSTITUTION OCCURS? IS THERE A PROBLEM OF INDISCRIMINANT SUBSTITUTION OF PRODUCTS BY PHARMACISTS IN STATES EVEN WHEN 'NO SUBSTITUTION' IS REQUESTED, AND ARE PRODUCTS NOT RATED AS BIOEQUIVALENT BEING SUBSTITUTED? SHOULD FDA GET INVOLVED IN THESE ISSUES?

These concerns were expressed by some speakers at the Hearing:

- Substitution is appropriate when there is significant savings to the consumer, when the consumer has the opportunity to discuss substitution with the physician and when the consumer will assume the risk of substituting a product. (Stoffer, p. 709 and 710)

- Substitution is taking place despite a physician's direction that there be "no substitution" on the prescription. I believe there are inferior formulations on the market and I have little control over what my patients receive unless they are made aware of their right to insist on the prescription as written by their physician. (O'Connor, p. 677-680, and see Section VI, followup)

- The patient may receive a different size, shape or color tablet from the product that he or she has been taking and may receive a tablet different again (in size, shape, and color) when refilling his prescription. This practice may create patient confusion. (Lipson, p. 694)

TASK FORCE CONCLUSION

FDA does not regulate the practice of pharmacy or medicine. Regulation of these professions is properly within a state's purview. The states are free to use FDA's bioequivalence determinations and therapeutic equivalence evaluations or not use them. Depending on individual product selection laws, some states develop their own formularies of interchangeable drug products. Each state has its own requirements regarding substitution. Thirty-eight states and the District of Columbia have permissive substitution and 12 have mandatory substitution. Forty states require patient consent for substitution. Commissioner Young stated that

"...we can in no way substitute federal judgment for state responsibility, and in no way substitute, in my opinion, state and federal responsibility for the responsibility of the physician. To do so would be, in my opinion, utter folly."

All states prohibit pharmacists from making substitutions of products when "DAW" (Dispense as Written) or some similar instruction is written by the physician. The Task Force concludes that allegations of violations of these prohibitions are appropriately within the jurisdiction of the states. Unauthorized substitution should be brought to the attention of the appropriate state authorities for any necessary action. These issues are not federal issues.

TASK FORCE RECOMMENDATION

The Task Force recommends that the Agency encourage physicians and pharmacists to make patients aware of the possibilities of drug substitution with their patients to avoid potential patient confusion when a different color tablet is dispensed, for example.

The Task Force encourages pharmacists and physicians to discuss with their patients the potential non-therapeutic differences of different brands and trade dress of products before the patient receives the product. Special efforts should be made to inform the elderly patient. The Agency should work with organizations like the AARP to disseminate advice to pharmacists and physicians and should encourage the states and drug industry to do so. The Agency could also accomplish this in a program similar to the "Talk About Prescriptions" Campaign sponsored by the National Council on Patient Information and Education.

C-6. WHAT SHOULD THE REQUIREMENTS BE FOR APPROVING BETTER FORMULATED COPIES OF POORLY BIOAVAILABLE INNOVATOR PRODUCTS?

The question of how the FDA should deal with generic drugs where the innovator is poorly bioavailable was brought up at least seven times during the Hearing (pp. 297, 485, 605, 687, 741 & 744, 748, and 754). Representative comments included:

- If the proposed formulation matches the innovator product in bioequivalence only at a lower dosage strength, then this lower strength should be approved and rated BP. All differences should be handled within the labeling. (AAPS Task Force, p. 605)

- Surely we can reach the intellectual level of considering that a reduced dose of a "superbioavailable" product might be equivalent to a well-established but incompletely available standard dosage form. (Gibaldi, p. 748)

TASK FORCE CONCLUSION

The Task Force is aware of only a handful of approved products on the market that are considered to be poorly bioavailable. This does not appear to be a major and immediate public health problem because:

1) each of the poorly formulated products was approved on the basis of clinical investigations demonstrating its safety and efficacy; and

2) each of these poorly formulated products has been on the market for several years without documented safety and efficacy problems.

FDA is prepared to approve generic products where the innovator is poorly available and the generic product matches the bioavailability of a more fully bioavailable formulation and produces blood levels equivalent to those of the innovator product when given at a lower dose. Such a product would be considered bioinequivalent to the innovator product under the petition provisions [Section 505(j)(2)(C)] of the Act. (see attachment 13)

TASK FORCE RECOMMENDATION

The Task Force recognizes that each of the few cases in which the innovator product is poorly bioavailable presents a unique circumstance and the Agency should use the petition [Section 505(j)(2)(C)] or other procedures to encourage the marketing of fully bioavailable products.

C-7. WHAT WOULD BE THE SIGNIFICANCE OF ONE DOCUMENTED GENERIC FAILURE?

- Several people have commented on the lack of any documented failures of approved generic drugs. I would not say (or put my company on record as saying) that if we find one documented failure, generic substitution will end. (Hayden, p. 674)

The issue of documented failures of approved generic drugs is discussed in detail in section C-3. In that section the emphasis is on the documentation of a failure and the fact that failures can and do occur for all products - innovator and generic alike. That is to say all drugs do not work in all people. And, it is difficult to document and distinguish a drug product failure from the failures of a drug in a single patient.

As explained in section C-3, a single report of the therapeutic failure of an approved generic product does not mean that all units of that generic drug are therapeutically inferior to the brand name product. Another way to look at this issue, however, is to ask - what would it mean if an approved product that was determined to be bioequivalent under current criteria and recommended as substitutable by the Agency is shown, by adequate documentation, e.g., a pattern of failures, not to have the same therapeutic effect as another product? The Agency is fully committed to investigate the reasons why this occurred and to take whatever action is necessary to correct the problem and minimize the public's exposure to the product. Finally, the Agency would reexamine the approval process for the particular product involved and, as is discussed in section B-1, would modify its bioequivalence criteria for the specific product involved, if necessary.

TASK FORCE CONCLUSION

The Task Force concludes that there is no reason to doubt the fundamental principle that drug products delivering comparable blood levels of a therapeutic moiety in bioequivalence tests in normals will generally yield comparable therapeutic results. There are known differences among patients, such as gut transit time or gastric pH that could, combined with differences between products, such as pH dependency of dissolution, theoretically yield differences in performance of products in certain patients. Whether this hypothesis actually is manifested clinically in any significant way has not been shown. A distinction must be drawn between a single case of a patient who does not respond to a drug product and evidence that a drug product is not performing. Virtually all products are, from time to time, the subject of isolated reports of therapeutic failures. The Agency looks particularly for patterns of such reports or cases which may indicate a generalized problem with a drug product or a batch of the product. The documentation of a single instance of clinical inequivalence does not, in the Task Force's view, undermine the much wider experience that shows bioequivalence testing to be an excellent predictor of clinical performance. A product failure, on the other hand, would necessitate that the Agency investigate thoroughly and take steps to deal with the particular case and others that might arise from similar circumstances.

V. COMMENTS FROM CONSULTANTS ON TASK FORCE REPORT

As part of the evaluation of the testimony heard at the Hearing, a draft of the Task Force report was sent to two of the outside consultants for their review and comments. (The third consultant was unable to review the report due to health reasons.) Both consultants generally agreed with the conclusions and recommendations in the report. They both said that the Task Force report addressed all the key issues raised at the Hearing. They suggested minor revisions in the tone and wording of several sections, and these revisions were incorporated into the final report. (see attachment 14)

In addition, there were two major issues with which the consultants differed from the Agency. The first issue had to do with the allowed 20% difference between generic and reference products. (issue B-1) One consultant agreed with the Agency; the other consultant believed that the Agency should modify its position and require that mean AUC values be within 10% rather than within 20%. After discussion, the Task Force concluded that the Agency should consider the feasibility of adding an additional nonstatistical criteria for the mean difference of AUC to be $\pm$ 10%.

The second issue deals with the means for obtaining outside input on general bioequivalence issues. One consultant said that the Agency should consider establishing a bioequivalence advisory panel as called for by some speakers. (issue C-2) The second consultant did not support the idea of a separate bioequivalence advisory panel, but favored the Agency alternatives of augmenting existing advisory panels to deal with bioequivalence issues. The Task Force agrees that the Agency should broaden outside input through more public forums on bioequivalence, and consider the ways of obtaining outside input.

VI. APPENDIX - Notes and Followup

Followup on claims of unauthorized substitution:

Two physicians speaking at the Hearing, (O'Connor p. 677-86 and Stoffer p. 707-38) cited examples where they had specifically written "no substitution" on the prescription, yet the patient still received the generic version of the drug. FDA's Division of Federal-State Relations followed up on these complaints and sent an inquiry to the appropriate authorities in the two states involved, (Wisconsin and Michigan) for investigation. In Wisconsin, the state investigator contacted Dr. O'Connor, to discuss his concerns; however, Dr. O'Connor failed to provide the names of specific violators. In Michigan, the state investigator sent a letter to Dr. Stoffer, but never received a followup response.

Followup on Material Promised to the Commissioner

All presenters were asked to submit copies of their talks and their slides to the Public Docket. (see attachment 15) Several speakers from the floor, and several presenters assured Commissioner Young that they would submit copies of their remarks and/or data referred to, but not presented at the Hearing. On December 24, 1986, the Notice in the Federal Register (51 FR 46721) appeared inviting additional comments, particularly comments that would supplement remarks made at the Hearing. Most of the supplemental material promised to Commissioner Young was not received and letters were sent to the following people requesting this information. (see attachment 16)

List of Drugs Cited

The following drugs were cited by various speakers during the Bioequivalence Hearing as examples of products that are not bioequivalent and/or not therapeutically interchangeable. Some of these products were cited as well-known examples of bioequivalent problem drugs, while the others were specific drugs listed as bioequivalent that some presenters believed were not bioequivalent. In some cases, data was presented to support their claim, while others were just cited as examples.

1. Examples cited of bioequivalence problem drugs

digoxin	sulfonylureas
dexamethasone	prednisone
quinidine gluconate	furosemide
ibuprofen	phenytoin
warfarin	haloperidol
diazepam	tolazamide
levothyroxine	chlorpromazine

2. Discussion

Most of the problems with the drugs listed above are known to FDA and have previously been investigated by the Agency. Digoxin is a pre-1938 drug which has not been evaluated for bioequivalence. Dexamethasone and prednisone are both DESI-review drugs with known bioequivalence problems. Dexamethasone products are not rated by FDA as bioequivalent. Prednisone products are rated as bioequivalent based on submission of in vitro dissolution testing data following an FDA study that showed a correlation between in vitro and in vivo data. Furosemide, warfarin, quinidine gluconate and phenytoin are all drugs that have previously been reported to FDA as not bioequivalent or having bioequivalence problems. These products and claims have all been investigated by FDA during the last few years and their bioequivalence issues are documented and well-known. All questions regarding the bioequivalence of these products have been satisfactorily answered by the Agency. Ibuprofen, haloperidol and sulfonylureas were cited as drugs with bioequivalence problems but no specific data were cited. Chlorpromazine is a multi-source drug product not rated as bioequivalent by FDA. The presenter cited data collected at the VA Hospital in Atlanta that reported a number of therapeutic failures and problems involving the substitution of generic chlorpromazine products which was thoroughly investigated by the FDA and found to be unsubstantiated and erroneous. The diazepam data cited by one presenter has been submitted to the Agency and reviewed by the Divisions of Biopharmaceutics and Bioequivalence. (see attachments 17 and 18) In addition, the FDA has contracted with the University of Tennessee to conduct a study on the effect of achlorhydria on drug absorption, including such drugs as diazepam.

The tolazamide data has been presented before to the Agency as well as to State Formulary boards. The Agency reviewed the data from Upjohn on tolazamide and found it interesting but retrospective in nature and mostly anecdotal. At a February 1986 meeting of the Technical Advisory Council for the Illinois Formulary, Mr. Gohdes from Upjohn indicated that the firm had done a second bioequivalence study. He indicated that their results did not agree with Dr. McDermott's clinical experience regarding inequivalence and that the firm had no new evidence to present. The generic firm involved (Zenith) has done its own clinical study in response to the accusations presented and does not reach the same conclusions on the differences in rate of absorption seen. (see attachment 6)

At the same Illinois Formulary meeting, Dr. Robert Buford from Searle presented the results of a bioequivalence study done on disopyramide phosphate in patients. When patients were switched from the innovator to the generic product, no differences were found in free or total disopyramide levels, AUC or half-life values for the products. Dr. Buford stated that based on this study, switching patient from innovator to generic product did not represent a medical hazard. Dr. Buford did express some personal reservations about indiscriminant switching between products at the pharmacy level without the physician being informed, however.

The problem with the bioinequivalence of various levothyroxine drug products is well known to FDA. This involves different pre-1938 drug products not rated as bioequivalent which according to the presenter, are being substituted for each other in the State of Michigan.

One presenter cited a list of more than 20 drugs which he claimed are being interchanged for the brand name drug in the State of Wisconsin and which he claims has caused therapeutic failures and are therefore not bioequivalent (including intravenous drug products). None of his claims included any data or support, and cannot be confirmed by the Agency. (see followup, P 45)

VII. LIST OF ATTACHMENTS

1. Memo from Deputy Commissioner Norris to Dr. Peter Rheinstein establishing Task Force. Memo from Dr. Rheinstein to Task Force members requesting their participation.

2. "FDA Speaks Out About Generic Drug Quality," NABP Newsletter, April, 1986, p. 53-54.

3. "Bioequivalence of Generic Thioridazine Drug Products - The FDA Viewpoint", Michael R. Hamrell, Marilyn N. Martinez, Shrikant V. Dighe & Paul D. Parkman, Drug Intell & Clin Pharm. 1987, 21:362-369.

4. Transcript of the Proceedings of the FDA Bioequivalence Hearing.

5. Memo to the Bioequivalence Task Force from FDA's Division of Biometrics - Statistical Background.

6. Summary of Zenith's study comparing tolazamide and Tolinase in patients.

7. Letter to Senator Hatch answering questions on the generic approval process.

8. FDA's Response to a Citizen Petition from Hoffmann La Roche (Docket No. 85P-0097/CP and PSA).

9. Draft Guidances on Waiver Policy for changes in formulation and Criteria for Waiver of in vivo bioavailability studies. Division of Bioequivalence, 1986.

10. Memo to the Bioequivalence Task Force from FDA's Division of Biometrics - Statistical Issues.

11. "Generic Drugs and the Prescribing Physician," S.L. Nightingale and J.C. Morrison, JAMA. 1987, 258:1200-1204.

12. Citizen Petition from Sonnenreich & Roccograndi (Docket No. 85P-0568/CP) and FDA's Response.

13. Speech presented by Dr. Peter H. Rheinstein at the 26th Annual International Industry Pharmacy Conference in Montgomery, Texas, February 15-19, 1987.

14. Letters from Drs. Gibaldi and Barr (consultants to the Task Force).

15. Index to contents of Docket number 86N-0251.

16. Followup to Participants Requesting Submission of Additional Information.

17. Diazepam Study Review by Division of Biopharmaceutics.

18. Diazepam Study Review by Division of Bioequivalence.

D A
TALK PAPER
FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
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REPORT ON BIOEQUIVALENCE OF GENERIC DRUGS

FDA has released the report of its Bioequivalence Task Force, a committee formed to study issues posed at a hearing Sept. 29-Oct. 1, 1986, on the agency's bioequivalence program and generic drugs in general.

The following may be used to answer questions.

FDA does not require manufacturers of a generic drug to repeat all the studies carried out by the maker of the original drug. But generic manufacturers must submit evidence to show that the generic, which has the same active ingredients, is bioequivalent to the original, that is that it will act in the body in the same manner, and to the same degree, as the original product.

The bioequivalence hearing was chaired by Commissioner Young and Deputy Commissioner Norris and was attended by more than 800 representatives of academia, industry, the medical profession and the government. It was held to afford all parties an opportunity to present their views.

At the conclusion of the hearing, Commissioner Young noted a lack of scientific data to back many of the concerns expressed regarding bioequivalence testing. He left the record open so the agency could receive

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additional presentations and views. The chairmen then appointed the task force to review all of the issues raised. (See Talk Paper T86-74, Oct. 15, 1986.)

In its report the Task Force states that the underlying fundamental principle that "drug products delivering comparable blood levels of a therapeutic substance yield comparable therapeutic results" is scientifically sound and that it sees no need to recommend major changes in the way FDA approves drug products.

The Task Force report supports the long-standing policy that if a drug product is declared by the agency to be therapeutically equivalent, a physician, in managing a patient, can feel secure that authorizing substitution of that product for any other therapeutically equivalent drug will provide the same intended effect.

The Task Force notes that there are occasions when a properly manufactured, handled and administered drug fails to have its intended effect, whether it is a generic or brand-name product. However, the Task Force adds, it is extremely unlikely in such cases that another make of the drug -- whether original or generic -- would have had a different effect.

The report also discusses other issues raised at the meeting:

-- The possible effects on drug action of different inactive ingredients, called excipients, in products is assessed by current bioequivalence studies. The possibility that a patient might be allergic to a particular inactive ingredient is currently being addressed by labeling programs of the Pharmaceutical Manufacturers Association, the Generic Pharmaceutical Industry Association, the National Association of Pharmaceutical Manufacturers and the Proprietary Association.

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— Some have argued that testing of generics should be required in patients instead of being conducted on healthy volunteers, but "it is preferable to subject healthy people, rather than patients, to the rigors of blood sampling and other discomforts of bioequivalence testing." According to the report, illnesses may actually interfere with accurate bioequivalence determinations.

-- Wide variations between name brand drugs and generics approved as therapeutically equivalent have been alleged, but the mean bioavailability difference between innovator products and generics is just 3.5 percent. (This is an insignificant difference if you consider that clinical studies of effectiveness often have difficulty detecting differences in dose of even 50 percent or more.) Critics who theorize that one FDA standard might permit variations in potency that would permit one generic to be 80 percent of the original drug and another to be 120 percent do not take into account all the criteria FDA uses. The Task Force urges that FDA criteria -- and any exceptions made to them because of special circumstances -- should be made more widely available. It notes that FDA is dropping a rule-of-thumb called the 75/75 rule as a decisional tool in favor of a precise statistical tool, the 90 percent confidence interval. (The 75/75 rule deemed a generic to be bioequivalent if at least 75 percent of test subjects developed blood levels of the drug that were 75 to 125 percent of what developed with the original drug.) The Task Force also recommends study of use of an additional criterion as an extra assurance of uniformity.

— The Task Force agrees that the Orange Book, the official list of FDA-approved drug products, should show whether a rating of therapeutic

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bioequivalence is based on in vivo studies (studies done in people) or in vitro studies (those done by lab tests) or both.

Dr. Peter H. Rheinstein, director of FDA's Office of Drug Standards, chaired the 19-member Task Force. Its report is available from FDA's Dockets Management Office, Room 4-62, 5600 Fishers Lane, Rockville, Md. 20857.

Commissioner Young, in accepting the report, noted that parts of it are already being implemented; the 75/75 rule, for example, was being phased out even before the 1986 hearing. Dr. Young said that the rest of the report will be implemented as soon as possible.

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